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Efficacy and safety of antiretrovirals in HIV-infected patients with cancer

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Abstract

At 30 years into the HIV infection epidemic, the optimal antiretroviral (ARV) regimen for infected patients with cancer remains unknown. We therefore sought to retrospectively study different ARV regimens used in this population. Data from HIV-infected patients seen at The University of Texas MD Anderson Cancer Center in Houston, Texas, USA, from 2001 to 2012 were reviewed. Patients received nucleoside reverse transcriptase inhibitors (NRTIs) plus protease inhibitors (PIs), non-NRTIs (NNRTIs), integrase strand-transfer inhibitors (INSTIs), or combinations of these. A total of 154 patients were studied. Most patients were male (80%), white (51%) and had haematological malignancies (HMs) (58%). NRTIs were combined with PIs (37%), NNRTIs (32%), INSTIs (19%) or combinations of these (11%). INSTIs were the most commonly used in patients with HM and in those receiving high-dose steroids or topoisomerase inhibitors ($p < 0.05$). Side-effects occurred in 35%, 14%, 3% and 6% of patients receiving PIs, NNRTIs, INSTIs and combinations, respectively (p 0.001). Grade 3–4 adverse events were uncommon. Multivariate logistic regression analysis demonstrated that INSTIs and NNRTIs were nine times (95% confidence interval (CI), 1.4–50.8) and 11 times (95% CI, 1.9–64.7) more likely to be effective at 6 months, respectively, than PIs. This is the largest reported analysis studying different ARV regimens in HIV-infected cancer patients. Combinations that included PIs were the least favourable. NNRTIs and INSTIs had comparable efficacy, but INSTIs appeared to be the better tolerated ARVs in patients with HM or those receiving various chemotherapeutic agents.

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Introduction

Several studies have suggested that the rates of acquired immunodeficiency syndrome (AIDS)-related cancers (e.g. Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and cervical cancer) have decreased greatly but that the incidence of non-AIDS-associated malignancies (e.g. cancers of the head and neck, lung, kidney, liver, gastrointestinal tract, anus, and skin (squamous cell carcinoma, basal cell carcinoma, and melanoma), Hodgkin lymphoma and leukaemia) in patients with chronic human immunodeficiency virus (HIV) infection have increased [1–4]. Regardless of the type of cancer in HIV-infected patients, malignancies now account for about 33% of all HIV-related deaths [5,6].

The need for treatment of cancer and HIV infection with concurrent antineoplastic agents and antiretrovirals (ARVs) is increasingly common [7]. Use of such simultaneous therapy reduces morbidity associated with opportunistic infections and improves overall survival rates in patients with HIV-related malignancies [8]. For example, concurrent ARV-based treatment and chemotherapy improves long-term outcomes in patients with AIDS-associated lymphoma [9,10].

Initiation and optimization of ARV-based therapy are recommended for HIV-infected cancer patients [11], but the optimal ARV regimens for these patients are unknown. Treating cancer in patients with HIV receiving ARVs is complicated because of a dearth of clinical understanding of potential drug interactions among cytotoxic and targeted antineoplastic agents and ARVs [3,7]. Combining antineoplastic agents and ARVs is accompanied by the potential for drug accumulation, overlapping toxic effects, and harmful effects of chemotherapy on immune status, decreasing the efficacy of one or both classes of drugs [4,7,8]. As a consequence, little information exists regarding the concomitant treatment of HIV infection and cancer, as HIV-infected patients are typically excluded from clinical trials of chemotherapeutic agents [7].

Clinicians caring for HIV-infected cancer patients are still in search of ARVs that are safe and effective in this population as guidelines for which ARVs to use in the setting of HIV and cancer are lacking. Therefore, in the present study, we retrospectively assessed the efficacy and safety of various ARVs in either treatment-naïve or previously treated HIV-infected patients who had cancer or underwent haematopoietic stem cell transplantation (HSCT) at The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

Materials and Methods

All HIV-positive patients with any type of cancer (AIDS- and/or non-AIDS-defining malignancies) seen from January 2001 to December 2012 were identified by searching institutional databases. Individual patient charts were reviewed for demographics, past medical history, date of HIV and cancer diagnosis, cancer type, co-infections, history of opportunistic infections, use of chemotherapy or immunosuppressive regimens, cancer treatment with associated complications, CD4+ lymphocyte count, HIV viral load, duration of ARV regimen, virological response to ARV regimen and its potential side-effects, and outcome.

Only patients who made regular clinic visits (at least two in a 6-month period), and whose treatment was initiated or monitored by MD Anderson infectious diseases specialists, were included. ARV-naïve or ARV-treatment-experienced adults with HIV/AIDS were included. The patients' ARV regimens were identified by searching the Division of Pharmacy database. Variations in CD4 T-cell count were not used as indicators of treatment response, as they can be affected by malignancies or their treatment (e.g. chemotherapy, prednisone). Likewise, changes in haematological parameters while on ARVs were not analysed because of the overlapping effects of many cancers or antineoplastic agents on bone marrow function. The sponsor of the study had no role in study design, data collection, analysis or interpretation, or manuscript writing. Our protocol was approved by the MD Anderson Institutional Review Board.

Clinically relevant drug interactions (either predictable or not) were defined as those resulting in adjustment of doses or discontinuation of co-administered agents. Specific clinically relevant interactions of ARVs with drugs commonly used to treat cancer were identified. These drugs included antifungal triazoles (e.g. voriconazole and posaconazole), immunosuppressants (tacrolimus and cyclosporine) and antineoplastic agents (e.g. alkylating agents, anthracyclines and taxanes). Clinical stage of HIV infection was defined as previously described [12]. ARV efficacy was defined as the absence of virological failure (HIV RNA $\geq$200 copies/mL $\geq$ 6 months on an ARV regimen initiated or monitored at MD Anderson) or virological rebound (two consecutive plasma HIV RNA >200 copies/mL after virological suppression) [1]. The 6-month follow-up period began at the time of initial evaluation at our centre.

Outcomes of the treatments were reviewed in terms of safety, drug interactions and ARV efficacy. The primary endpoints were safety and tolerability, including adverse events, side effects and clinically relevant drug interactions. The Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events was used for grading the intensity of clinical events and laboratory abnormalities. The secondary endpoint was efficacy. The data analyses consisted of four-group comparisons including patients treated with nucleoside reverse transcriptase inhibitors (NRTI) backbone plus (i) PIs, (ii) NNRTIs, (iii) INSTIs or (iv) combinations of these. The chi-square or Fisher exact test was used to compare categorical variables. If a significant result (p 0.05) was detected, pairwise comparisons between individual groups were performed to identify the significant differences. The Kruskal–Wallis test was used to compare continuous variables. If a significant result was detected, the Wilcoxon rank sum test was used for the pairwise comparisons. The α levels of the *post hoc* pairwise comparisons were adjusted using the sequential Bonferroni method to control for type I errors. In addition, logistic regression analysis was used to identify predictive factors for efficacy and mortality. All tests except those in the pairwise comparisons were two-sided at a significance value of 0.05. The statistical analyses were performed using the SAS software program (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

A total of 154 cancer patients seen during the study period with HIV infection and available ARV data were included in the

analysis. Most of the patients were male (n = 123, 80%) and white (n = 79, 51%). The most common underlying malignancy was haematological (n = 90, 58%), primarily NHL (n = 64, 71%). Among the 64 patients with solid tumours, most had gastrointestinal cancer (n = 20, 31%). Nineteen patients (12%) underwent HSCT, and most of the transplants were autologous (n = 15, 79%). INSTIs were the most common ARVs used in patients with haematological malignancies (p 0.001; Table 1).

The most common NRTIs were tenofovir (104 patients, 68%) or abacavir (22 patients, 14%) in combination with emtricitabine or lamivudine. NRTI backbone was combined with PIs (57 patients, 37%), NNRTIs (50 patients, 32%), INSTIs (30 patients, 19%), or a combination of these (17 patients, 11%) (Table 1). Raltegravir was the only INSTI available during the study period.

The different cancer treatment modalities administered to HIV-infected patients receiving ARVs are depicted in Table 2. Chemotherapy agents used included taxanes (paclitaxel and docetaxel), vinca alkaloids (vincristine, vinblastine and vinorelbine), topoisomerase inhibitors (etoposide, irinotecan and topotecan), alkylating agents (cyclophosphamide, ifosfamide, dacarbazine, procarbazine, melphalan, cisplatin, carboplatin, carmustine, oxaliplatin and mechlorethamine), antimetabolites (methotrexate, 5-Fluorouracil, cytarabine, fludarabine, gemcitabine, decatinib, hydroxyurea, azacitidine and capecitabine), antitumour antibiotics (doxorubicin, bleomycin and mitomycin), targeted therapy (rituximab, cetuximab, gefitinib, bortezomib, ofatumumab, trastuzumab, panituximab, erlotinib and sorafenib), endocrine/hormone therapy (anastrozole, leuprolide and bicalutamide), and miscellaneous agents (L-asparaginase). Statistically or numerically, INSTIs were the most common ARVs used in patients concomitantly receiving high-dose steroids, topoisomerase inhibitors, alkylating agents or antimetabolites (Table 2).

The 6-month efficacy rates of INSTIs and NNRTIs were comparable (96% and 97%, respectively; p >0.99). Both rates were superior to that of PIs (65%; p 0.005 and p 0.001, respectively) (Table 3). Baseline HIV RNA levels (odds ratio (OR), 1.33; 95% CI, 0.5–3.9; p 0.61) and nadir CD4 cell count (OR, 1.0; 95% CI, 0.99–1.0; p 0.2) were not associated with 6-month efficacy after adjusting for ARV groups. Multivariate logistic regression analysis of predictive factors for ARV efficacy at 6 months demonstrated that the type of ARVs concomitantly used (p 0.004) was significantly associated with ARV efficacy at 6 months. Compared with PIs, INSTIs were nine times (95% CI, 1.4–50.8) more likely to be effective at 6 months, whereas NNRTIs were 11 times (95% CI, 1.9–64.7) more likely to be effective at 6 months.

Infectious disease specialists, oncologists and pharmacists reviewed the ARV regimens to minimize drug interactions. In this controlled setting, clinically relevant drug interactions were uncommon, occurring only in those who received PIs (4%). We observed only two clinically significant drug interactions: one in a patient receiving a PI regimen and cyclosporine and the other in a patient receiving nevirapine and mirtazapine. In 11 (7%) patients, the physicians changed the initial ARV regimen in anticipation of potential interactions with chemotherapeutic or antifungal agents (e.g. voriconazole). Specifically, in nine patients, physicians switched from NNRTIs (efavirenz and etravirine) or PIs (ritonavir-boosted darunavir or lopinavir) to INSTIs. In two patients, they switched from an NNRTI (efavirenz) to a PI. ARV-related side-effects occurred in 35%, 14%, 3% and 6% of patients receiving PIs, NNRTIs, INSTIs or combinations, respectively (p 0.001). Grade 3–4 adverse events were uncommon. There was no correlation between ARV duration and occurrence of side-effects after accounting for ARV groups (OR, 1.0; 95% CI, 0.99–1.02; p 0.17), probably due to the small number of adverse events in some groups (Table 4). None of the patients had immune reconstitution syndrome.

Numerically, interruption of ARV-based treatment was less common in patients receiving INSTIs than in those receiving PIs or NNRTIs (7%, 28% and 26%, respectively). The ARV/chemotherapy combinations that were demonstrated to be safe are shown in Fig. 1.

The overall mortality rates were 46%, 36%, 13% and 41% in the patients receiving PIs, NNRTIs, INSTIs and combinations, respectively (p 0.03). Progression of cancer was the most common cause of death in all treatment groups. Logistic regression analysis of predictive factors for death showed that cancer status (p <0.0001) was the only factor independently associated with death.

Discussion

At 30 years into the HIV infection epidemic, the optimal ARV regimen for infected patients with cancer remains unknown. In the present study, the largest analysis of different ARVs administered to HIV-infected patients with cancer to date, we made several important observations. First, PI regimens are less efficacious than NNRTI and INSTI regimens in this patient population. Second, the efficacy of NNRTIs is comparable with that of INSTIs. Third, NNRTI and INSTI regimens have a better safety profile than PI regimens. Fourth, INSTIs are well tolerated in patients with haematological malignancies or those receiving concomitant steroids or various chemotherapeutic agents and were chosen when potential interactions with chemotherapeutic or antifungal agents were anticipated. These findings should aid infectious diseases specialists and

TABLE 1. General characteristics of the HIV-infected patients with cancer according to ARV regimen (*n* = 154)

Characteristic	Number of patients (%)				p Value
	NRTIs + INSTI (*n* = 30)	NRTIs + PI (*n* = 57)	NRTIs + NNRTI (*n* = 50)	Combination (*n* = 17)[a]	
Median age, years (range)	51 (21–68)	50 (29–74)	48 (30–82)	53 (38–67)	0.49
Male sex	24 (80)	42 (74)	41 (82)	16 (94)	0.3
Race					
White	19 (63)	30 (53)	22 (44)	8 (47)	0.55
Black	8 (27)	21 (37)	15 (30)	6 (35)	
Hispanic	2 (7)	5 (9)	10 (20)	3 (18)	
Others	1 (3)	1 (2)	3 (6)	0	
Type of cancer					
Haematological	25 (83)	24 (42)	34 (68)	7 (41)	<0.001[b]
NHL	17 (68)	19 (79)	24 (71)	4 (57)	
HL	3 (12)	3 (13)	5 (15)	1 (14)	
Leukaemia	5 (20)	1 (4)	3 (9)	1 (14)	
Myeloma	0	1 (4)	2 (6)	1 (14)	
Solid tumour	5 (17)	33 (58)	16 (32)	10 (59)	
GI	2 (40)	11 (33)	4 (25)	3 (30)	
Prostate	0	5 (15)	3 (19)	1 (10)	
Lung	0	2 (6)	3 (19)	2 (20)	
Breast	0	1 (3)	4 (25)	0	
Melanoma	0	1 (3)	0	2 (20)	
Others[c]	3 (60)	13 (39)	2 (13)	2 (20)	
HSCT	5 (17)	2 (4)	10 (20)	2 (12)	0.04[d]
Autologous	2 (40)	2 (100)	9 (90)	2 (100)	
Allogeneic	3 (60)	–	1 (10)	–	
Cancer status					
Complete remission	16 (53)	26 (46)	28 (56)	9 (53)	0.95
Progressive disease	9 (30)	20 (35)	17 (34)	6 (35)	
Partial remission	1 (3)	1 (2)	1 (2)	0	
Stable disease	4 (13)	10 (18)	4 (8)	2 (12)	
HIV infection status					
Positive before cancer diagnosis	17 (57)	46 (81)	32 (64)	17 (100)	0.009
Diagnosed along with cancer	10 (33)	9 (16)	16 (32)	–	
ARV status at cancer diagnosis					
Naïve	15 (50)	18 (33)	23 (46)	0	0.003
Experienced	15 (50)	37 (67)	27 (54)	17 (100)	
Length of ARV therapy, months, median (range)	19 (8–272)	48 (6.5–206)	32 (7–132)	65 (2–208)	0.008[e]
Clinical stage of HIV infection at baseline					
Stage 1	4 (13)	11 (19)	9 (18)	3 (18)	0.11
Stage 2	7 (23)	10 (18)	6 (12)	5 (29)	
Stage 3 (AIDS)	19 (64)	27 (47)	23 (46)	6 (35)	
Stage unknown	0 (0)	9 (16)	12 (24)	3 (18)	
Baseline HIV-RNA, copies/mL, median (range)	1100 (0–872 000)	386 (0–4 530 000)	52 (0–4 230 000)	47 (0–1 260 000)	0.15
<100 000	24 (80)	39 (71)	34 (69)	10 (59)	0.48
Baseline CD4 cell count, cells/mm^3, median (range)	120 (4–888)	167 (3–1,143)	181 (7–1444)	264 (21–865)	0.59
Nadir CD4 cell count, cells/mm^3, median (range)	86 (3–390)	63 (2–724)	75 (1–646)	100 (3–298)	0.92
HIV resistant mutations	7 (58)	10 (77)	4 (44)	1 (50)	
Treatment naïve	7 (100)	5 (50)	4 (100)	0 (0)	
RT mutations only	2 (29)[f]	0 (0)	0 (0)	–	
PI mutations only	1 (14)[g]	4 (80)[h]	4 (100)[i]	–	
Both mutations	4 (57)[j]	1 (20)[k]	0 (0)	–	
Treatment experienced	0 (0)	5 (50)	0 (0)	1 (100)	
RT mutations only	–	2 (40)[l]	–	0 (0)	
PI mutations only	–	0 (0)	–	0 (0)	
Both mutations	–	3 (60)[m]	–	1 (100)[n]	

HL, Hodgkin's lymphoma; GI, gastrointestinal.
[a]PIs only (four patients), HIV fusion inhibitors (one patient), NRTI backbone plus NNRTIs plus PIs (three patients), NRTI backbone plus PIs plus INSTIs (one patient), NNRTIs plus PIs plus INSTIs (three patients), NNRTIs plus INSTIs (one patient), NRTI backbone plus NNRTIs plus INSTIs (one patient), PIs plus INSTIs (two patients), or NNRTIs plus PIs (one patient).
[b]NRTI backbone + INSTI vs. NRTI backbone + PI, p <0.001; NRTI backbone + INSTI vs. combination, p 0.003; NRTI backbone + PI vs. NRTI backbone + NNRTI, p 0.007.
[c]Other solid tumours: cancer of nasopharynx (*n* = 1), urethra (*n* = 1) and squamous cell carcinoma (SCC) of oral cavity (*n* = 1) in NRTIs + INSTI group; SCC of mandible (*n* = 2), SCC of cervix (*n* = 2), SCC of vulva (*n* = 2), SCC of larynx (*n* = 2), SCC of skin (*n* = 2), SCC of tongue (*n* = 1), SCC of maxillary sinus (*n* = 1) and cancer of thymus (*n* = 1) in NRTIs + PI group; basal cell carcinoma of nasal vestibule (*n* = 1) and SCC of paranasal sinuses (*n* = 1) in NRTIs + NNRTIs group; metastatic carcinoma of unknown primary (*n* = 1) and SCC of tongue (*n* = 1) in combination group.
[d]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.047; NRTI backbone + PI vs. NRTI backbone + NNRTI, p 0.01.
[e]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.01; NRTI backbone + INSTI vs. combination, p 0.02; NRTI backbone + PI vs. combination, p 0.06; NRTI backbone + NNRTI vs. combination, p 0.008.
[f]NNRTI mutation (V108I (*n* = 2)).
[g]PI mutation (L10V).
[h]NRTI mutations (D67N, K219Q, M184I, T69N, T215V), NNRTI mutations (K103S, V90I, V118I (*n* = 2), V179D/E), PI mutations (A71T, I62V (*n* = 2), K20R, L63P (*n* = 2), M36I (*n* = 2), V77I (*n* = 2), I93L).
[i]PI mutations (A71T, I13V (*n* = 3), I62V (*n* = 2), I93L, L10I, L63P (*n* = 2), L63P/T (*n* = 2), V77I (*n* = 2)).
[j]NNRTI mutations (V90I), PI mutations (A71T, I13V, L63P, M36I).
[k]NNRTI mutations (Y181C, 103N, 135WT/M, 188WT/C).
[l]NRTI mutations (70R, 67N, 184V, L210W, M41L, M184V (*n* = 2), T215Y), NNRTI mutations (K103N, L100I), PI mutations (46I, 71T, 147A, 154V, 163V, K20R, L63P, L89M, L10I (*n* = 2), V32I, V77I, V82A).
[m]PI mutations (A71V, L10I, M36I (*n* = 2)).
[n]NRTI mutations (L210W, M41L, M184I, T69D, T215Y), NNRTI mutations (K103N, Y181C), PI mutations (A71T, I13V, I15V, I54V, K20I, L10I, L63P, L90M, M46I, Q58E, V71I).

TABLE 2. Chemotherapy, immunosuppressive agents and radiotherapy administered to HIV-infected patients with cancer receiving ARVs

Treatment	Number of patients (%)				p Value
	NRTIs + INSTI (*n* = 30)	NRTIs + PI (*n* = 57)	NRTIs + NNRTI (*n* = 50)	Combination (*n* = 17)	
Cytotoxic drugs	26 (87)	37 (65)	39/49 (80)	12 (71)	0.12
Taxanes	1 (3)	4 (7)	2 (4)	3 (18)	0.24
Vinca alkaloids	13 (43)	14 (25)	16 (32)	3 (18)	0.2
Topoisomerase inhibitors	13 (43)	8 (14)	10 (20)	3 (18)	0.016[a]
Alkylating agents	21 (70)	26 (46)	23 (46)	6 (35)	0.07[b]
Antimetabolites	16 (53)	13/50 (26)	16 (32)	7 (41)	0.08[c]
Antitumour antibiotics	12 (40)	14 (25)	17 (34)	3 (18)	0.28
Targeted therapy	10 (33)	18 (32)	18 (36)	5 (29)	0.95
Endocrine/hormone therapy	0	1/50 (2)	4 (8)	0	0.35
Miscellaneous agents	1 (3)	0	0	0	0.31
Investigational agents	0	1 (2)	1 (2)	1 (6)	0.61
Immunosuppressive drugs					
Corticosteroids	26 (87)	39/54 (72)	40/46 (87)	13/15 (87)	0.19
>600 mg (prednisone equivalent), mg	24/26 (92)	20/34 (59)	28/36 (78)	9/13 (69)	0.023[d]
Other immunosuppressants	2 (7)[e]	3 (5)[f]	0	0	0.27
Radiotherapy	11 (37)	27/55 (49)	20 (40)	9 (53)	0.55

[a]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.002; NRTI backbone + INSTI vs. NRTI backbone + NNRTI, p 0.026.
[b]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.03; NRTI backbone + INSTI vs. NRTI backbone + NNRTI, p 0.04; NRTI backbone + INSTI vs. combination, p 0.02.
[c]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.014.
[d]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.004.
[e]Tacrolimus in both patients.
[f]Sirolimus, mycophenolate acid and cyclosporine in one patient each.

TABLE 3. Efficacy of ARV-based treatment of HIV infection in cancer patients

Efficacy	NRTI + INSTI (%)	NRTI + PI (%)	NRTI + NNRTI (%)	Combination (%)	p Value
At 6 months	23/24 (96)	30/46 (65)	30/31 (97)	7/9 (78)	<0.001[a]
Naïve	12/12 (100)	9/15 (60)	18/18 (100)	–	<0.001[b]
Experienced	11/12 (92)	20/30 (67)	12/13 (92)	7/9 (78)	0.2
At 1 year	7/7 (100)	15/25 (60)	22/24 (92)	8/9 (89)	0.017[c]
Naïve	5/5 (100)	5/8 (63)	9/9 (100)	–	0.04
Experienced	2/2 (100)	9/16 (56)	13/15 (87)	8/9 (89)	0.18

Non-compliant patients were excluded.
[a]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.005; NRTI backbone + PI vs. NRTI backbone + NNRTI, p 0.001.
[b]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.02; NRTI backbone + PI vs. NRTI backbone + NNRTI, p 0.005.
[c]NRTI backbone + PI vs. NRTI backbone + NNRTI, p 0.01.

oncologists in clinical decision-making regarding selection of the most appropriate ARVs for HIV-infected cancer patients receiving chemotherapy.

At present, guidelines are lacking for ARV-based treatment in cancer patients receiving chemotherapy, partly because patients with HIV infection are excluded from studies of cancer drugs [13]. Therefore, the clinician's dilemma is how to administer therapy to patients who need treatment with anticancer drugs in light of the propensity for interactions of these drugs with ARVs [7].

In several studies, researchers have investigated how ARVs are metabolized and how they induce and inhibit the activity of various enzymes involved in drug metabolism [3,14]. The majority of ARVs (NNRTIs, PIs and chemokine receptor antagonists) are metabolized via the cytochrome P450 (CYP450) pathway [10]. Likewise, many chemotherapeutic agents are metabolized by CYP450. Therefore, the potential for interactions of these agents with ARVs is great. Bidirectional interactions of ARVs with other classes of anticancer agents, including alkylating agents, corticosteroids, epipodophyllotoxins, taxanes, tyrosine kinase inhibitors and vinca alkaloids, also may occur [7]. Anthracyclines, antimetabolite agents, antitumour antibiotics and platinums undergo non-CYP450 routes of elimination and are unlikely to be altered by ARV [7]. A drug interaction is predicted between ritonavir, which induces the phase I detoxifying enzyme CYP3A2, and sorafenib, a substrate of this enzyme [15].

In addition, some ARVs are known to induce over-expression of CYP450 enzymes. For instance, nevirapine, efavirenz, ritonavir and tipranavir induce CYP450 3A4 expression [3]. This induction of enzyme expression can increase the elimination from the body of other drugs that undergo similar metabolism. Metabolism-related drug interactions involving NRTIs are minimal because these agents are not eliminated by the CYP450 system, nor do they induce or inhibit CYP450 enzymes [8]. PIs and NNRTIs are extensively metabolized by

TABLE 4. Side-effects in HIV-infected patients with cancer receiving ARVs

Variable	NRTI + INSTI	NRTI + PI	NRTI + NNRTI	Combination	p
Side-effects[a] (%)	1/30 (3)	17/49 (35)	7/49 (14)	1/17 (6)	0.001[b]
ARV only (%)	0/1 (0)	8/17 (47)	2/7 (29)	1/1 (100)	0.037[c]
ARV + chemotherapy (%)	1/1 (100)	9/17 (53)	4/7 (57)	0/1 (0)	0.09
ARV + chemotherapy + other drugs (%)	0/1 (0)	0/17 (0)	1/7 (14)	0/1 (0)	>0.99
ARV + progressive cancer (%)	0/1 (0)	5/17 (29)	3/7 (43)	0/1 (0)	1.0
Developed co-infections while on ARV (%)	0/1 (0)	5/17 (29)	3/7 (43)	1/1 (100)	1.0
Length of ARV therapy, months, median (range)	8 (8–8)	65 (28–204)	34 (10–108)	208 (208–208)	0.17
Type of side-effects					
CNS (%)	0/1 (0)	0/17 (0)	3/7 (43)	0/1 (0)	
Bizarre dreams (%)	–	–	2/7 (29)	–	
Dizziness (%)	–	–	1/7 (14)	–	
GI (%)	1/1 (100)	4/17 (24)	0/7 (0)	0/1 (0)	
Diarrhoea (%)	0/1 (0)	3/17 (18)[d]	–	–	
Nausea (%)	0/1 (0)	1/17 (6)[d]	–	–	
GI discomfort (%)	1/1 (100)	0/17 (0)	–	–	
Hepatobiliary (%)	0/1 (0)	2/17 (12)	1/7 (14)	0/1 (0)	
Elevated transaminases (%)	–	1/17 (6)[d]	1/7 (14)[d]	–	
Hyperbilirubinaemia (%)	–	1/17 (6)[e]	0/7 (0)	–	
Skin rash (%)	1/1 (100)[d]	0/17 (0)	1/7 (14)[d]	0/1 (0)	
Renal (%)	0/1 (0)	2/17 (12)	0/7 (0)	0/1 (0)	
Acute renal failure (%)	–	1/17 (6)[e]	–	–	
Nephrolithiasis (%)	–	1/17 (6)[d]	–	–	
Lipodystrophy (%)	0/1 (0)	1/17 (6)	1/7 (14)	1/1 (100)	
Fat accumulation (%)	–	1/17 (6)[d]	–	1/1 (100)[d]	
Lipoatrophy (%)	–	–	1/7 (14)[e]	–	
Hyperlipidaemia (%)	0/1 (0)	3/17 (18)	1/7 (14	0/1 (0)	
Cholesterol (%)	–	3/17 (18)[f]	–	–	
Triglycerides (%)	–	–	1/7 (14)[d]	–	
Neuropathy (%)	0/1 (0)	4/17 (24)[d]	0/7 (0)	0/1 (0)	
Osteopenia (%)	0/1 (0)	1/17 (6)[d]	0/7 (0)	0/1 (0)	

CNS, central nervous system; GI, gastrointestinal.
[a]One patient may develop more than one side-effect; all side-effects reported occurred within 6 months of initial evaluation.
[b]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.001; NRTI backbone + PI vs. NRTI backbone + NNRTI, p 0.02.
[c]NRTI backbone + INSTI vs. NRTI backbone + PI, p 0.021.
[d]Grade 1–2 side-effects.
[e]Grade 3–4 side-effects.
[f]Two of the three patients who received NRTI + PI and developed hyperlipidaemia had grade 2 hypercholesterolaemia and one patient had grade 3 hypercholesterolaemia.

and induce or inhibit the CYP450 system, creating a high potential for drug interaction [7]. Maraviroc is a substrate of both the CYP450 3A enzyme and ABCB1 transporter and is susceptible to interactions with many drugs [7]. Furthermore, to varying degrees, all PIs inhibit CYP450 3A4 activity [3]. In comparison, raltegravir undergoes glucuronidation via UDP-glucuronosyltransferase 1A1 (UGT1A1) and has less potential for drug interactions than PIs and NNRTIs [16].

To better understand potential drug interactions in and the tolerability of combined ARV-based therapy and chemotherapy, the AIDS Malignancy Consortium, a National Cancer Institute-sponsored cooperative group, launched a series of clinical studies in HIV-infected patients with refractory cancers. These trials have focused on new targeted chemotherapeutic agents [4]. The investigators stratified HIV-infected patients into three groups based on their ARV regimens: (i) non-NNRTI-based therapy, (ii) non-ritonavir PI-based therapy and (iii) ritonavir-based therapy; studies are in progress [17]. In the present study, we found that PI regimens had a poor safety profile and a significantly lower efficacy in comparison with those of NNRTIs and INSTIs. PI-based treatment appears to greatly potentiate the myelotoxicity of chemotherapy [18]. Our results support the inclusion of raltegravir-based regimens in future studies analysing the safety of concomitant use of chemotherapeutic agents and ARVs. Elvitegravir, one of the other US Food and Drug Administration-approved INSTI, is principally metabolized via the CYP450 pathway. Therefore, interactions of it with several commonly used anticancer drugs are expected. Dolutegrevir seems to have a safe drug interaction profile, making it a potential agent in the treatment of cancer patients with HIV infection [19].

Few studies have addressed the combined use of chemotherapeutic agents and ARVs. Most of the studies have focused on assessment of tumour response and progression with the use of different chemotherapeutic agents, excluding details such as type of ARV used and virological outcome [15,20–22]. An unanswered therapeutic question is whether the addition of cytotoxic chemotherapy to ARV-based treatment causes significant toxic effects or compromises HIV-directed care.

Our results regarding the concomitant use of several classes of ARVs are reassuring. However, the clinical importance of complex drug interactions in HIV-infected cancer patients receiving ARVs and chemotherapy should not be considered trivial, and patients receiving concomitant chemotherapy and ARV regimens should be closely monitored. In a study of two patients with HIV-associated KS who received paclitaxel along with PI regimens, life-threatening toxic effects developed in both of them [23]. In the present study, a multidisciplinary team reviewed the ARV regimens to prevent the occurrence of clinically relevant drug interactions.

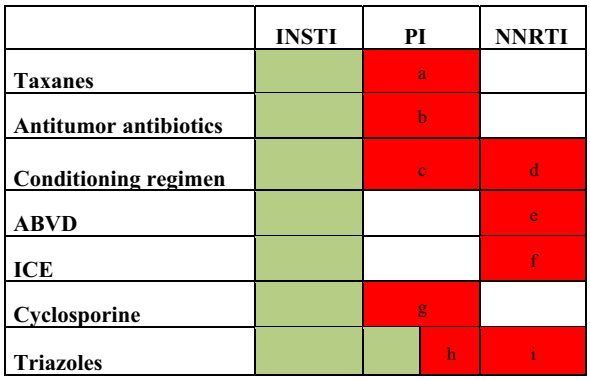

FIG. 1. Combinations of ARVs and chemotherapeutic agents used in the study. Combination used safely. Combination adjusted or changed. [a]Chemotherapeutic agent, docetaxel; ARV, ritonavir-boosted darunavir; action, ARV changed to raltegravir. [b]Chemotherapeutic agent, doxorubicin; ARV, etravirine; action, ARV changed to raltegravir. [c]Chemotherapeutic agents, fludarabine and melphalan; ARV, ritonavir-boosted lopinavir; action, ARV changed to raltegravir. [d]Chemotherapeutic agents, fludarabine and busulfan; ARV, efavirenz; action, ARV changed to raltegravir. [e]Chemotherapeutic agents, doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD); ARV, efavirenz; action, ARV changed to raltegravir. [f]Chemotherapeutic agents, ifosfamide, carboplatin and etoposide (ICE); ARV, efavirenz; action, ARV changed to raltegravir. [g]Immunosuppressive agent, cyclosporine; ARV, ritonavir-boosted lopinavir; action, cyclosporine changed to sirolimus. [h]Triazole, posaconazole; ARV, ritonavir-boosted darunavir; action, ARV changed to raltegravir. [i]Triazole, voriconazole; ARV, efavirenz; action, ARV changed to raltegravir or atazanavir.

Our study results should be interpreted with caution given the study's retrospective nature, small sample size, lack of information on time of cancer diagnosis, detailed cancer chemotherapy and changes in supportive care that modified cancer outcome (potentially impacting efficacy of INSTIs that were most recently introduced), and lack of pharmacokinetic assessment. However, results of pharmacokinetic studies of chemotherapy and ARVs do not always correlate with clinical outcome. For example, in a previous study of 34 patients with advanced HIV-associated KS who received paclitaxel and ARVs, paclitaxel exposure was higher in patients taking PIs than in those not taking them, but the increased drug exposure did not correlate with efficacy or toxicity of paclitaxel [24]. Differences in mortality are likely to reflect the outcome of the different types of cancer, as the most common cause of death in all treatment groups was progression of cancer.

In conclusion, administration of an INSTI or NNRTI regimen but not a PI regimen resulted in increased safety and suppressed viral replication without causing significant adverse events in HIV-infected patients who had cancer or had undergone HSCT. When interactions of chemotherapeutic and antifungal agents are anticipated, specific INSTIs appear to be the ARVs of choice. Larger prospective studies are required to further define the toxicity profiles of HIV-infected cancer patients receiving chemotherapy. Such studies should help aid the development of specific guidelines for treatment in this patient population.

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Transparency Declaration

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